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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: July 15, 2002

SUBJECT: Tebufenpyrad - Report of the Cancer Assessment Review Committee

FROM: Jessica Kidwell
Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

TO: Pamela Hurley, Toxicologist
Registration Action Branch 2
Health Effects Division (7509C)

George LaRocca, Product Manager
Susan Stanton, PM Team Reviewer
Registration Division (7505C)

The Cancer Assessment Review Committee met on May 15, 2002 to evaluate the carcinogenic potential of Tebufenpyrad. Attached please find the Final Cancer Assessment Document.

cc: K. Dearfield
R. Hill
J. Pletcher
Y. Woo

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
TEBUFENPYRAD
PC CODE 090102

FINAL REPORT
July 15, 2002
TXR NO. 0050025

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

Tebufenpyrad Cancer Assessment Document Final Report

DATA PRESENTATION: Pamela Hurley
Pamela Hurley, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

William Burnam
Marion Copley
Virginia Dobozy
Nancy McCarroll
Tim McMahon
Esther Rinde
Joycelyn Stewart
Clark Swentzel
Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

John M. Pletcher, Pathology Consultant See attached sheet
Virginia Fornillo, Statistical Analysis

DATA PRESENTATION:

Pamela Hurley, Toxicologist

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EXECUTIVE SUMMARY

On May 15, 2002, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of tebufenpyrad.

Tebufenpyrad was administered in the diet to 55 male and 55 female F344 rats at concentrations of 0, 5, 20, 150, or 300 ppm (0, 0.21, 0.82, 6.52, 13.43 mg/kg/day for males and 0.26, 1.01, 8.13, 16.95 mg/kg/day for females) for 105 weeks; and to 64 male and 64 female CD-1 mice at 0, 30, 500, or 1000 ppm (0, 3.6, 64.4, and 132.1 mg/kg/day for males and 0, 4.2, 71.3, and 162.0 mg/kg/day for females) for 78 weeks.

The CARC concluded that tebufenpyrad showed suggestive evidence of carcinogenicity based on the following:

- Male rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 300 ppm dose group with the controls, for hepatocellular adenomas, both at $p< 0.01$. The incidence at the high dose (300 ppm) exceeded the historical control range. The CARC considered the increase in benign liver tumors to be treatment-related in males. No hepatocellular carcinomas were observed in any group, including controls.

- Female rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 150 ppm dose group with the controls, for hepatocellular adenomas, both at $p< 0.05$. However, no dose-related increase in these tumors was noted at the high dose (300 ppm). The incidence at 150 ppm was just outside the historical control range; and the incidence at 300 ppm was within the historical control range. No hepatocellular carcinomas were observed in any group, including controls.

- In rats, dosing at the highest level was considered by the CARC to be adequate, but not excessive, in both sexes based on decreased body weight gains in males (21%) and females (33%), clinical chemistry changes, increased liver weights, and liver hypertrophy.

- There was no treatment-related increase in any tumors in male and female mice.

- In mice, dosing at the highest level (1000 ppm) was considered by the CARC to be adequate, but not excessive, in both sexes based on decreased body weight and body weight gain in males and females (61-75% of controls) after 52 and 78 weeks of treatment, decreased food efficiency, and a dose-related increased incidence of stomach dysplasia in both sexes.

- Tebufenpyrad was not mutagenic in bacterial or mammalian cell gene mutation assays. However, tebufenpyrad induced weak but reproducible clastogenic effects in human lymphocytes after prolonged exposure to cytotoxic concentrations. There was no increase in the frequency of micronucleated PCEs in bone marrow and no induced DNA damage in mammalian cells or in bacteria. Based on the findings the level of concern for in vitro clastogenesis is low because it was only seen after prolonged exposure to cytotoxic concentrations and was not manifested in the in vivo cytogenetic assay up to lethal doses. The submitted studies were acceptable and satisfy the guideline requirements for mutagenicity data. No further testing is required at this time. The Committee has no concern for mutagenicity.

- No appropriate structural analogues were located for comparison purposes.

- There are no mode of action studies available at this time.

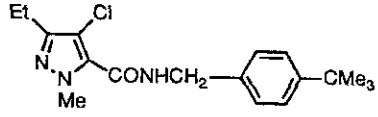
In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July 1999), the CARC classified tebufenpyrad into the category **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"**, and therefore, the quantification of human cancer risk is not required.

I. INTRODUCTION

On May 15, 2002, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Program met to evaluate the carcinogenic potential of tebufenpyrad. This was the first time this compound was assessed for carcinogenicity by the CARC.

I. BACKGROUND INFORMATION

Tebufenpyrad is a new active ingredient broad spectrum acaricide/insecticide from the pyrazole class of chemicals. No appropriate structural analogues could be located. The PC Code is 090102 and the CAS number is 119168-77-3. The structure is as follows:



Tebufenpyrad is proposed to be used on non-edible greenhouse ornamental crops. It is anticipated that there will be chronic dermal and inhalation exposure.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Oncogenicity and Toxicity Study by Dietary Administration of Tebufenpyrad to F-344 Rats for 104 Weeks

Reference: Mitchell, D. (1992) MK-239 (AC 801,757): Combined Oncogenicity and Toxicity Study by Dietary Administration to F-344 Rats for 104 Weeks. Life Science Research Ltd. Eye Suffolk IP23 7PX England. LSR Report No. 91/0988, February 25, 1992, MRID 43309320. Unpublished.

A. Experimental Design

MK-239 (99.5% a.i.) was administered in the diet to 55 male and 55 female F344 rats at concentrations of 0, 5, 20, 150, or 300 ppm (0, 0.21, 0.82, 6.52, 13.43 mg/kg/day for males and 0, 0.26, 1.01, 8.13, 16.95 mg/kg/day for females) for 105 weeks. An additional ten animals of each sex in each dose group were included for interim sacrifice at 53 weeks.

B. Discussion of Tumor Data

Survival Analysis

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Tebufenpyrad in either male or female rats (Memo, L. Brunsman, 4/16/02, TXR No. 0050673).

Tumor Analysis

Male rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 300 ppm dose group with the controls, for hepatocellular adenomas, both at $p < 0.01$. The incidence of hepatocellular adenomas in males was 0/54, 0/55, 0/53, 4/54, and 10/54 for the 0, 5, 20, 150, or 300 ppm dose levels, respectively. These were expressed as the number of tumor bearing animals/number of animals examined, excluding those that died or were sacrificed before week 54. It also excludes accidental death animals. No hepatocellular carcinomas were observed in any group, including controls.

Female rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 150 ppm dose group with the controls, for hepatocellular adenomas, both at $p < 0.05$. The incidence of hepatocellular adenomas in females was 0/53, 2/53, 0/54, 5/54, and 3/54 for the 0, 5, 20, 150, or 300 ppm dose levels, respectively. These were expressed as the number of tumor bearing animals/number of animals examined, excluding those that died or were sacrificed before week 55. It also excludes accidental death animals. No hepatocellular carcinomas were observed in any group, including controls.

The statistical analyses of both sexes were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 1 and 2 and for tumor analysis results.

Table 1. Tebufenpyrad - F344 Rat Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p-values)

	Dose (ppm)				
	0	5	20	150	300
Adenomas# (%)	0/54 (0)	0/55 (0)	0/53 (0)	4/54 (7)	10[a]/54 (19)
p =	0.0000**	1.0000	1.0000	0.0590	0.0006**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54. Also excludes accidental death animals.

#No carcinomas were observed.

[a]First adenoma observed at week 87, dose 300 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Tebufenpyrad - F344 Rat Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p-values)

	Dose (ppm)				
	0	5	20	150	300
Adenomas# (%)	0/53 (0)	2/53 (4)	0/54 (0)	5[a]/54 (9)	3/54 (6)
p =	0.0397*	0.2476	1.0000	0.0297*	0.1250

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55. Also excludes accidental death animals.

#No carcinomas were observed.

[a]First adenoma observed at week 106, dose 150 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data were provided for 5 intercurrent studies with the same route of administration and for which the animals were housed similarly. Historical control data were also provided for other studies; however, the housing and route of administration were different. Only ranges were provided. No individual values and no means were available. Tables of both are as follows:

Table 3: Intercurrent Control Data - Range of Tumor Incidence[a]

Tumor	Males		Females	
	Number Examined	Range (%)	Number Examined	Range (%)
Liver				
hepatocellular adenoma	510	0.0 - 8.0	510	0.0 - 8.0
hepatocellular carcinoma	510	0.0 - 2.0	510	0.0 - 2.0
Pituitary				
adenoma	502	6.0 - 48.0	502	22.9 - 61.7
carcinoma	502	0.0 - 8.0	502	0.0 - 16.0
Thyroids				
parafollicular cell adenoma	507	0.0 - 20.4	509	0.0 - 10.0
parafollicular cell carcinoma	507	0.0 - 8.2	509	0.0 - 8.2

a Extracted from Appendix 20 H (pages 2621-2624) of the study report.

Table 4: Historical Control Data - Range of Tumor Incidence[a]

Tumor	Males		Females	
	Number Examined	Range (%)	Number Examined	Range (%)
Liver				
hepatocellular adenoma	1579	0.0 - 12.0	1578	0.0 - 8.0
hepatocellular carcinoma	1579	0.0 - 2.0	1578	0.0 - 2.0
Pituitary				
adenoma	725	6.0 - 48.0	725	22.9 - 61.7
carcinoma	725	0.0 - 8.0	725	0.0 - 16.0

a Extracted from Appendix 20 I (pages 2625-2627) of the study report. These data include

singly housed studies and routes of administration other than dietary.
For comparison purposes with the historical control data, Table 5 provides the liver tumor incidences directly from the study report.

Table 5. Hepatocellular Adenomas In Male and Female Rats fed MK-239 for 104 weeks

Lesions	Concentration (ppm)				
	0	5	20	150	300
Males					
Liver Hepatocellular adenoma	0/55	0/55	0/55	4/54 (7%)	10/55*** (18%)
Females					
Liver Hepatocellular adenoma	0/55	2/55	0/55	5/55*	3/55

Data taken from Table 17D and 18C, pp. 270-274, 277, MRID 43309320.
*p<0.05; **p<0.01, ***p<0.001

C. Non-Neoplastic Lesions

The incidences of notable nonneoplastic lesions are presented in Table 6. Statistically significant increases in the incidence of hepatocellular hypertrophy was seen in both male [6/54(11%) and 14/55 (25%)] and female rats [24/55 (44%) and 44/55 (80%)] fed the 150- and 300-ppm diets, respectively. The incidence of focal cystic degeneration in the liver was significantly increased in male rats receiving the 20- [16/55 (29%)] and 150-ppm [13/54(24%)] diets; no increase was observed at the 300-ppm dietary level; therefore, this lesion is probably not treatment related. Portal tract changes in the liver were statistically significantly increased at the 150- and 300-ppm dietary levels. Significant increases in the incidence of pancreatic acinar cell hyperplasia occurred in male [15/55 (27%) vs 1/54 (2%) in controls, $p<0.01$] and female rats [11/54 (20%) vs 1/54 (2%) in controls, $p<0.01$] fed the 300-ppm diet. In female rats, significant increases in the incidences of mammary gland acinar hyperplasia [11/55 (20%) vs 1/55 (2%) in control] occurred at the 300-ppm dietary level and in ovarian bursal cysts at the 150- and 300-ppm dietary level [11/55 (20%) and 10/55 (18%), respectively, vs 3/55 (5%) in controls]. There were no significant increases in incidence of lesions in animals sacrificed at 52 weeks except for the following: progressive (senile) nephropathy at the 150-ppm dietary level and parafollicular hyperplasia in the mandibular lymph nodes at the 300-ppm dietary level in female, and focal necrosis with inflammatory infiltrate in the liver of males receiving the 20- and 150-ppm diets. Because there were no similar increases in the main study, these lesions were not predictive of treatment-related effects for the main study. It is possible that the hepatocellular hypertrophy is related to the increase in hepatocellular adenomas in male rats; however, the increase was even more significant in female rats, in which there was not a significant increase in liver tumors.

Table 6. Selected nonneoplastic microscopic lesions in male and female rats fed MK-239 for 104 weeks

Lesions	Concentration (ppm)				
	0	5	20	150	300
Males					
Liver					
Hepatocellular hypertrophy	0/55	0/55	0/55	6/54**	14/55***
Portal tract change[a]	33/55	36/55	32/55	6/54***	3/55***
Focal cystic degeneration	4/55	5/55	16/55**	13/54*	8/55
Pancreas					
Focal acinar cell hyperplasia	1/54	0/55	2/55	4/55	15/55***
Testes					
Degen. of tubul. germ. epit.	9/55	4/55	9/55	2/55	1/54*
Females					
Liver					
Hepatocellular hypertrophy	0/55	0/55	1/55	24/55***	44/55***
Portal tract change[a]	11/55	12/55	16/55	2/55*	0/55***
Mammary gland					
Acinar hyperplasia	1/55	5/55	6/55	5/55	11/55**
Ductal hyperplasia	1/55	2/55	3/55	1/55	6/55
Ovaries					
Bursal cysts	3/55	6/55	5/55	11/55*	10/55
Pancreas					
Focal acinar cell hyperplasia	1/55	1/55	2/54	7/55	11/54**

Data taken from Table 16E, pp. 250-261, MRID 43309320.
[a]Includes proliferation of bile ducts, hyaline degeneration, and inflammation.
*p<0.05, **p<0.01, ***p<0.001

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The dosing was considered to be adequate but not excessive for both male and female rats. At the highest dose tested (300 ppm) males and females weighed less than controls throughout the study (up to 16% for males and 22% for females). Mean body weight gain was also significantly less than controls (21 and 33%, respectively, $p<0.01$) for males and females, respectively over the course of the study (weeks 0-104). The greatest difference in body weight gain at the 300-ppm dose level occurred during the first year of treatment in males as they gained only 80% as much weight as controls and during the second year of treatment in females as they gained only 36% ($p<0.01$) as much weight as controls. Alkaline phosphatase activity was significantly increased in males (120 to 183%, $p<0.001$ compared with controls) and in females (172 to 303%, $p<0.001$

compared with controls) from week 24 to termination at the highest dose tested. At termination of the main study, the absolute liver weight was significantly elevated in male (126%, $p<0.01$) and female (132%, $p<0.01$) rats compared with the corresponding control weights. The relative liver to body weights were also elevated at the same dose (147% for males and 167% for females). An increase in the incidence of hepatocellular hypertrophy (25 and 80% in males and females, respectively versus none in the control groups) was observed. These results are also supported by increased albumin/globulin ratios in both sexes. Lesions also occurred in the pancreas (focal acinar cell hyperplasia) in male (15/55 vs 1/54 in controls) and female rats (11/54 vs 1/55 in controls) and in the mammary gland (acinar hyperplasia) of female rats (11/55 vs 1/55 in controls).

In the 90-day oral toxicity study, MK-239 was administered to 10 F-344 rats/sex/group in the diet at dose concentrations of 0, 10, 100, or 400 ppm for 13 weeks. Additional groups of 10 control and 10 high-dose animals (5 per sex) were held for a 4-week recovery period. The average calculated MK-239 doses over the 13-week period for the 10, 100, and 400 ppm treatment groups were 0.7, 6.8, and 29 mg/kg/day for males, respectively, and 0.7, 7.3, and 32 mg/kg/day for females, respectively.

At 400 ppm, there were statistically significant differences in body weight gains (74% and 73% of control values for males and females, respectively), food conversion efficiency (12.9% and 6.6% compared with respective control values of 16.6% and 9.1% for males and females), and absolute (liver in both sexes) and relative organ weights (liver, kidney, brain, pituitary, lungs, heart, spleen, testes, and thymus in one or both sexes). At 100 ppm, alterations in organ weights, accompanied by changes in clinical chemistry parameters were observed; however, these responses are considered to be a non-adverse adaptive response to chemical treatment as they were not accompanied by histological changes in any organ. At 400 ppm, the decreased body weight gain, accompanied by the changes in organ weights were considered to be toxicologically significant effects.

Based on the results from the chronic/oncogenicity study in rats and the subchronic feeding study in rats, the high dose level of 300 ppm in the chronic/oncogenicity study is considered to be adequate.

2. Oncogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks

Reference: Mitchell, D.J., Aughton, P. and Holmes, P. (1994) MK-239 (AC 801,757): Oncogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks. Life Science Research Ltd., Eye, Suffolk IP23 7PX, England. Study Number: 91/0808, February 14, 1994. MRID 43309316. Unpublished.

A. Experimental Design

In a 78-week oncogenicity feeding study, MK-239 was administered in the diet to 64 male and 64 female CD-1 mice per group at 0, 30, 500, or 1000 ppm. Twelve male and 12 female mice from each group were sacrificed after 52 weeks of treatment to provide interim data. The concentrations corresponded to average doses of about 0, 3.6, 64.4, and 132.1 mg/kg/day for males; and 0, 4.2, 71.3, and 162.0 mg/kg/day for females.

B. Discussion of Tumor Data

A summary of common neoplasms seen at terminal sacrifice in this study is given in Table 7. No increases in tumor incidences were seen in treated animals at any dose. The frequency and types of tumors observed are within the normal range expected for mice of this strain and age. The only trend observed was a decrease in the number of animals with liver carcinomas at the 500 and 1000 ppm doses compared with the control group.

Table 7. Incidence of Mice Fed Mk-239 in Their Diet for 78 Weeks with Neoplastic Lesions (Including Decedents)

Affected Organ or Tissue/ Lesion	Treatment Group/Exposure Level (ppm)							
	Males				Females			
	0	30	500	1000	0	30	500	1000
Liver/Hepatocellular carcinoma	9[a] 17.3%	7 13.5%	0**	1** 1.9%	0	0	0	0
Lungs/Pulmonary adenoma	2 3.8%	2 3.9%	2 3.8%	2 3.8%	1 1.9%	1 1.9%	2 3.8%	3 5.8%
Lungs/Pulmonary carcinoma	2 3.8%	5 9.8%	4 7.7%	5 9.6%	4 7.7%	6 11.5%	4 7.7%	3 5.8%
Hemopoietic/Lymphoma	2 3.8%	2 3.8%	1 1.9%	0	5 9.6%	5 9.6%	5 9.6%	4 7.7%
Total no. Primary neoplasms	20	21	12	12	20	18	18	13
Total no. mice with 1 or more tumors	19 36.5%	20 38.5%	11 21.2%	12 23.1%	18 34.6%	18 34.6%	17 32.7%	12 23.1%
Total no. mice with 1 or more benign tumors	3 5.8%	3 5.8%	4 7.7%	6 11.5%	6 11.5%	2 3.8%	6 11.5%	5 9.6%
Total no. mice with 1 or more malignant tumors	17 32.7%	17 32.7%	8 15.4%	6 11.5%	12 23.1%	16 30.8%	12 23.1%	8 15.4%

Data taken from Table 13E, pp. 0200-0202; Tables 14A, B, and C, pp. 0203-0205, Appendix 13, pp. 0874-0910; Appendix 14, pp. 1100-1141, MRID No. 433093-16.

[a]Number of animals with tumor(s)/Percent occurrence in animals examined (n = 52)

**p<0.01, Fisher exact test by reviewer.

C. Non-Neoplastic Lesions

A summary of selected findings obtained by microscopic examination of tissues and organs from mice fed diets containing MK-239 for 78 weeks is given in Table 8. The incidence of animals found with erythrocytes and erythrophagocytosis in the sinuses of the mesenteric lymph nodes decreased with the 500 and 1000 ppm doses in males and with all doses in females compared to the control groups. The decreases were significant for males at both doses and for females at 1000 ppm; however a clear dose-response relationship was not seen. There was also a decrease in periacinar hepatocytic fatty vacuolation in males at all doses and in females at 500 and 1000 ppm. The decreased vacuolation of hepatocytes in males was not dose-dependent or statistically significant, but in females, it appeared to be dose-related at 500 and 1000 ppm and was statistically significant at the high dose. The incidence of extramedullary hemopoiesis in the spleens was significantly decreased in male mice at 30 and 500 ppm MK-239, but was not decreased compared to the control group at 1000 ppm. There were increases in the incidence of dysplasia seen in the glandular stomach of treated mice that were statistically significant at all doses in females compared to the control group. However, a clear dose-response relationship was not seen. Similar findings were seen in the animals that died or were killed prior to study termination or at the 52-week interim period. The toxicological significance of these findings is questionable.

Table 8 . Incidence of Mice Fed -239 in Their Diet for 78 Weeks with Non-neoplastic Lesions (52 Mice/group Including Decedents)

Affected Organ or Tissue/Lesion	Treatment Group/Exposure Level (ppm)							
	Males				Females			
	0	30	500	1000	0	30	500	1000
Mesenteric Lymph Node/ Erythrocytes & Erythrophagocytosis in Sinuses	14 29.2%	17 34.0%	5* 10.6%	6* 12.2%	14 28.0%	7 14.3%	7 13.7%	5* 10.6%
Liver/Hepatocytic Fatty Vacuolation	10 19.2%	4 7.7%	6 11.5%	6 11.5%	10 19.2%	10 19.2%	3 5.8%	1** 1.9%
Spleen/Extramedullary Hemopoiesis	26 51.0%	16* 30.8%	11** 21.6%	24 46.2%	8 15.7%	4 7.8%	4 7.7%	3 5.9%
Glandular Stomach/Dysplasia	7 13.7%	8 15.4%	10 19.6%	12 23.5%	1 1.9%	9* 17.3%	8* 15.4%	8* 15.4%

Data taken from Table 12E, pp. 0183-0194, MRID No. 43309316.
[a]Number of animals with lesion/ % occurrence in animals examined (n=50-52)
* $p<0.05$, ** $p<0.01$ Significantly different from controls.

D. Adequacy of Dosing for Assessment of Carcinogenicity

The dosing was considered adequate but not excessive for assessment of carcinogenicity in both sexes. The group mean body weights were significantly ($p<0.05$) decreased at 1000 ppm after 28, 52 and 78 weeks of treatment in both sexes and also after 14 weeks of treatment in females. Male group mean body weights at 1000 ppm were 90% of the control group mean body weight at 52 weeks and 91% at 78 weeks; female group mean body weights were 87% of the control group mean body weights at 52 weeks and 85% at week 78. The group mean body weight gain was significantly ($p<0.01$) decreased in both sexes to 61-75% of the control weight gain at 1000 ppm after both 52 and 78 weeks of treatment. There was also decreased overall food efficiency in both sexes at the high dose (74% and 58% of the control groups in males and females, respectively). The platelet counts were significantly increased in females at 1000 ppm after 52 and 78 weeks of treatment (121 and 112% of control, respectively). The counts were slightly higher than the historic controls presented in the study, but were within the normal range reported for this strain of mouse by the Charles River Laboratories. Significant ($p<0.01$) increases in the group mean absolute and relative kidney and liver weights were seen in females at 1000 ppm (112 and 120% of controls for absolute weights, respectively; 129 and 139% of controls for relative weights, respectively). No treatment-related increase in the incidence of any lesion in the liver or kidney was found that corresponded to the organ weight changes. An increase in the incidence of thickened stomach wall from 1.9% in the controls to 15.4% in males at 1000 ppm was seen, however, there was no clear dose-response relationship. Increases in the incidences of glandular stomach dysplasia were seen on microscopic examination that were statistically significant in females at all dose levels compared to the control group (1.9% in controls, 17.3 15.4, and 15.4%, respectively at the low, mid, and high doses). However, female control animals in historical studies had an incidence of stomach dysplasia of 13.4%, which indicates that the statistical significance of this lesion in the current study is due to an unusually low incidence for stomach dysplasia in the female control group. The increase was not statistically significant in males (13.7% in controls, 15.4% at 30 ppm, 19.6% at 500 ppm, and 23.5% at 1000 ppm), but it appeared to be dose-dependent and was associated with the thickening of the stomach wall seen in males at 1000 ppm on gross examination.

IV. TOXICOLOGY

1. Metabolism

In a metabolism study (MRID 43309326), six groups, each containing a minimum of five male and five female Fisher rats, were given a single gavage dose of 10 or 50 mg/kg MK-239 (99% a.i., Lot 2332-260) containing approximately 800 kBq ^{14}C-labeled chemical. The radiolabel was at the 3 position of the pyrazole ring. Rats at both doses were killed 3, 8, 24, 72, or 168 hours post-dosing. Two additional groups, each with 4 male and 4 female rats whose bile ducts had been cannulated, received 10 mg/kg or 50 mg/kg test material and were killed 24 hours after treatment. An additional group of 5 male and 5 female rats were pretreated with unlabeled test material for 14 days before receiving 10 mg/kg radiolabeled MK-239. These rats were killed 7 days later. In

a preliminary study, no radiolabel was detected within 48 hours in the breath of two male rats treated with 10 mg/kg or 128 mg/kg test material. No intravenous studies were done due to solubility problems with the test material.

The results show >80% of the MK-239 was absorbed from the digestive system within 24 hours. The compound appeared to undergo rapid and extensive first-pass metabolism to primarily hydroxylated or carboxylated products with little of the parent compound appearing in the urine or feces. As a result, the test material was found within the stomach and intestinal tract, associated lymphatics, and the liver with lesser amounts found within the kidney. The test material was excreted primarily in the feces which accounted for ≥60% of the elimination; however, a significant portion was found in the urine (16-24%). More than 70% of the test material or its metabolites were eliminated within 72 hours of treatment and >90% was eliminated by 7 days. No accumulation of the parent compound or its metabolites was noted. A slight sex-specific difference in the metabolic disposition of the test material was found with male rats excreting more of the carboxylic acid metabolite on a relative basis while females tended to excrete more of the sulfate conjugate.

2. Mutagenicity

Tebufenpyrad was tested in a *Salmonella*/microsome plate incorporation assay, a forward mutation study at the HGPRT locus in Chinese hamster V79 cells in culture, a mouse bone marrow micronucleus assay, an unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes and a DNA repair differential growth inhibition assay. In these studies there was no evidence of induced reverse mutation in bacterial cells or forward mutation in mammalian cells. Tebufenpyrad induced weak but reproducible clastogenic effects in human lymphocytes but only after prolonged exposure to cytotoxic concentrations. There was no increase in the frequency of micronucleated PCEs in bone marrow and no induced DNA damage in mammalian cells or in bacteria. Based on the findings, the level of concern for in vitro clastogenesis is low because it was only seen after prolonged exposure to cytotoxic concentrations and was not manifested in the in vivo cytogenetic assay up to lethal doses. The submitted studies were acceptable and satisfy the guideline requirements for mutagenicity data. No further testing is required at this time.

In a *Salmonella*/microsome plate incorporation assay (MRID No. 43309321), *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 and *Escherichia coli* strain WP2(uvrA) were exposed to MK-239 at concentrations of 50, 158, 500, 1580 and 5000 µg/plate, with and without exogenous metabolic activation. Preparations for metabolic activation were made from Aroclor 1254 induced male CD rat livers. The test material was delivered in DMSO.

Cytotoxicity, as evidenced by a slight thinning of the background lawn of bacteria, was seen at 5000 µg/plate with all strains. Positive and solvent controls were acceptable. **There was no evidence of induced revertant colonies over solvent control values in any strain at any dose**

tested, either with or without S9 mix.

In a forward mutation study at the HGPRT locus in Chinese hamster V79 cells in culture (MRID No. 43309322, Batch No. 880222), cells were exposed to MK-239 (98.5%) under non-activated conditions at concentrations of 1.25, 2.5, 5, 10, 20, 30 µg/ml in the first assay and 2.5, 5, 10, 20, 30, 40 µg/ml in a second assay and under activated conditions to concentrations of 10, 20, 40, 60, 100, 150 µg/ml in the first assay and to 40, 60, 100, 150, 175, 200 µg/ml in a second assay. Preparations for metabolic activation were made from Aroclor 1254 induced male CD rat liver. The test material was delivered in DMSO.

MK-239 was tested to concentrations limited by cytotoxicity and solubility. Positive and solvent control values were appropriate. **No reproducible dose-related increase in mutation frequency was seen at the HGPRT locus in Chinese hamster V79 cells in this study, either with or without S9 mix.**

In a mouse bone marrow micronucleus assay (MRID #43309323), 5 CD-1 mice/sex/dose were administered single oral doses of MK-239 at 75, 150 or 300 mg/kg. The test material was delivered in aqueous 0.5% (w/v) carboxymethyl cellulose. Bone marrow cells were harvested at 24 hours post-treatment. Doses and harvest time were determined from the results of a preliminary toxicity test using 100, 200, and 400 mg/kg doses and from the results of a preliminary micronucleus test using 300 mg/kg doses and harvest times of 24, 48 and 72 hours post-treatment.

Lethargy, hunching, piloerection and slow, labored breathing were seen in all mice in the 24 hours following administration of 300 mg/kg of test material. One male and one female at this dose were found dead in their cages 2 hours post-treatment. There was no evidence of bone marrow cytotoxicity as determined by the polychromatic erythrocyte to normochromatic erythrocyte (PCE/NCE) ratio at any dose. The mean incidence of micronucleated PCEs (per 1000 PCEs scored) was 1.2 (0.0 - 3.0) for the vehicle control group and 0.4, 0.6 and 0.5 for the 75, 150 and 300 mg/kg groups (range 0.0 - 1.0 for each group), respectively. **There was no significant increase in the frequency of micronucleated PCEs in bone marrow after any dose of MK-239 tested in this study.**

Two independently performed *in vitro* cytogenetic assays utilizing human lymphocytes as the target cell line were included in this submission (MRID 43309324). In an *in vitro* mammalian cell cytogenetic assay reported in 1994, human blood lymphocytes in culture were exposed to MK-239 (98.8% a.i.) at concentrations of 6, 8, 20, 40, 60, 80 µg/ml without exogenous metabolic activation (S9 mix) with an exposure time of 21 hours and to 8.25, 11, 27.5, 55, 82.5, 110 µg/ml with S9 mix with an exposure time of 4 hours. Cells were evaluated for chromosomal aberrations at 20, 40 and 80 µg/ml without S9 mix and at 27.5, 55 and 110 µg/ml with S9 mix. A confirmatory test was conducted using concentrations comparable to those evaluated in the initial

test. An additional assay with a continuous exposure of 44 hours (without S9 activation) and a 20-hour continuous exposure with S9 activation was included.

In an *in vitro* mammalian cell cytogenetic assay reported in August 1990, human blood lymphocytes in culture were exposed to MK-239 (98.5% a.i.) at concentrations of 6.25, 12.5 and 25 µg/ml in the absence of S9 mix (2 hour exposure) and 12.5, 25 and 50 µg/ml in the presence of S9 mix (3 hour exposure). For both studies, preparations for metabolic activation were made from Aroclor 1254 induced rat liver and the test material was delivered in DMSO.

The test material was assayed to concentrations producing greater than a 50% depression of the mitotic index (MI). Positive and solvent control values were appropriate. In the 1994 study, no significant increase in chromosomal aberrations was seen at any concentration evaluated in the initial test, either with or without S9 mix. In the confirmatory 1994 assay, significant increases in chromosomal aberrations were seen at 20 and 40 µg/ml in the absence of a significant dose-response (primary sampling time without S9 mix) while a significant dose-response in the absence of a significant increase at any particular dose was noted at the delayed sampling time with S9 mix. Although some statistically significant increases in chromosomal aberrations were observed in MK-239 treated cells, failure to reproduce the results makes it unlikely that the increases are biologically significant. **In the 1994 study, there was no clear evidence of a biologically significant induction of chromosomal aberrations by MK-239 at any concentration tested in this study, either with or without S9 mix.**

In the 1990 study, in the presence of S9 mix, no significant increases in the mean aberrant cell frequencies over solvent control values were seen at any dose of MK-239. In the absence of S9 mix, significant increases in mean aberrant cell frequencies over solvent control values were seen at all doses of MK-239 ($p < 0.001$). The increase in mean aberrant cell frequency at the highest dose tested, 25 µg/ml (3% versus 0.3% in the solvent control cultures), was lower than the increases seen at the two lower doses (7%), presumably due to cytotoxicity since there was an 84% reduction in the MI at this level. The effect was, however, significant ($0.05 > p > 0.01$). **In the 1990 study, MK-239 showed clastogenic activity at all concentrations tested in the absence of S9 mix but at no concentration tested in the presence of S9 mix.**

Overall, the combined data from both studies indicate that without S9 activation, the compound induced variable but nevertheless reproducible significant increases in the percentage of aberrant cells in two of three experiments using treatment times of 20-24 hours. In general, levels causing $\approx \leq 40\%$ decrease in the MI were negative, whereas concentrations causing $\geq 42\%$ decrease in the MI induced significant effects with reproducibly flat dose response curves. Furthermore, the same type of aberrations (chromatid breaks) was induced in both studies. Based on these considerations, it is concluded that MK-239 exhibited reproducible but weak evidence of a clastogenic response but only after prolonged exposure to cytotoxic doses and only in the absence of S9 activation.

In an unscheduled DNA synthesis (UDS) assay in primary rat thepatocytes (MRID No. 43309325), cultures of primary hepatocytes from a male Sprague-Dawley rat were exposed to MK-239 at concentrations of 0.0977, 0.309, 0.977, 3.09 and 9.77 µg/ml. The compound was delivered in DMSO and the cells exposed to the test material for approximately 17 hours. MK-239 was tested to a cytotoxic concentration and positive and solvent control values were appropriate. Two independent experiments were conducted. Four independent cultures, rather than six as stated in the guidelines, were used for each test point and, prior to cell lysis, pairs of cultures were combined giving two replicate DNA extractions for each test point. The results were consistent within each experiment and showed no increase in tritiated thymidine incorporation over solvent control values at any concentration tested. The reduced number of replicate cultures is unlikely to have compromised the usefulness of the study. **As tested in this study, MK-239 did not induce DNA damage detectable by the UDS assay.**

In a DNA repair differential growth inhibition assay (MRID # 43320001), *Bacillus subtilis* strains H17(rec$^+$) and M45(rec$^-$) were exposed to MK-239 (98.9% a.i., Lot 8J-10) at doses of 200, 500, 1000, 2000, 5000 and 10,000 µg/filter paper disk/plate with and without exogenous metabolic activation. Preparations for metabolic activation were made from Aroclor 1254 induced male Sprague-Dawley rat livers. The test material was delivered in DMSO.

Positive controls, both with and without S9 mix showed appropriate preferential growth inhibition of the rec- strain (difference in diameter of growth inhibition zones of the rec$^-$ and rec$^+$ strains of 18 and 22 mm for Mitomycin C and 8 and 10 mm for 2 aminoanthracene). The negative control produced similar growth inhibition of both the rec$^-$ and rec$^+$ strains and the vehicle control showed no growth inhibition. No growth inhibition of either strain was seen at any dose of MK-239 tested in the presence of S9 mix. In the absence of S9 mix, slight growth inhibition (1 to 3 mm diameter growth inhibitory zone) was seen at doses of 500 through 5000 µg/disk in both strains but no growth inhibition was seen at 10,000 µg/disk in either strain. The differences in diameter of the growth inhibition zones for the two strains were 0 or 1 mm for all cultures except one culture at 500 µg/disk with a 2 mm difference. Where a difference was seen, the repair deficient strain had the largest zone of growth inhibition but the differences were not significant. **MK-239 did not induce preferential killing of the repair defective M45(rec-) strain at any dose tested, either in the presence or absence of S9 mix, indicating no ability to damage the bacterial DNA as tested in this study.**

3. Structure-Activity Relationship

Tebufenpyrad (PC Code 090102; CAS No.119168-77-3) belongs to the pyrazole class of chemicals. No appropriate structural analogues could be located for comparison purposes.

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

Rats

In a 90-day oral toxicity study (MRID 4330911), MK-239 (98.5% a.i., Lot 88022) was administered to 10 F-344 rats/sex/group in the diet at dose concentrations of 0, 10, 100, or 400 ppm for 13 weeks. Additional groups of 10 control and 10 high-dose animals (5 per sex) were held for a 4-week recovery period. The average calculated MK-239 doses over the 13-week period for the 10, 100, and 400 ppm treatment groups were 0.7, 6.8, and 29 mg/kg/day for males, respectively, and 0.7, 7.3, and 32 mg/kg/day for females, respectively.

At 400 ppm, there were statistically significant differences in body weight gains (74% and 73% of control values for males and females, respectively), food conversion efficiency (12.9% and 6.6% compared with respective control values of 16.6% and 9.1% for males and females), and absolute (liver in both sexes) and relative organ weights (liver, kidney, brain, pituitary, lungs, heart, spleen, testes, and thymus in one or both sexes). Hematology (decreases in hemoglobin, hematocrit, and mean corpuscular hemoglobin and volume in females and decreased platelets in males and females) and clinical chemistry parameters including alkaline phosphatase activity, proteins, cholesterol, triglycerides, and phospholipids were statistically significantly altered; however the magnitude of the change from control values was small. Many of these same clinical chemistry parameters were also statistically significantly altered in the 100 and 10 ppm treatment groups, although to a lesser extent. At 100 ppm, absolute liver (both sexes) and relative liver (both sexes), kidney (both sexes), and heart (males) weights were increased and were accompanied by changes in clinical chemistry parameters. These responses are a non-adverse adaptive response to chemical treatment as they were not accompanied by histological changes in any organ. At 400 ppm, the decreased body weight gain, accompanied by adaptive changes in relative organ weights, is a biologically important treatment-related effect as it was only partially reversible during a 4-week recovery period. **Under the conditions of this study, a NOAEL of 100 ppm (6.8 mg/kg/day for males and 7.3 mg/kg/day for females) was achieved. A LOAEL of 400 ppm in the diet (29 mg/kg/day for males and 32 mg/kg/day for females) was established based on decreases in body weight gain accompanied by changes in relative organ weights.**

Dogs

In a subchronic oral toxicity study [MRID 43309313], groups of five male and five female beagle dogs were given technical MK-239 [98.9% a.i., Lot J-10] in gelatin capsules at doses levels of 0 [empty gelatin capsules], 2, 10, or 20 mg/kg/day for 93 days [males]/91 days [females].

No animals died during the study. The most significant toxic effect of MK-239 was an increased incidence and duration of food vomiting and/or diarrhea in both sexes at 10 and 20 mg/kg/day, particularly during the first two months of treatment. This was accompanied by slight, statistically non-significant increases in the incidence of colon focal mucosal congestion in 10 and 20 mg/kg/day males (2/5 and 3/5, respectively, vs. 0/5 for controls), in stomach focal mucosal

congestion in 20 mg/kg/day males (2/5 vs.1/5 for controls), and in stomach focal mucosal edema in 20 mg/kg/day females (1/5 vs. 0/5 for controls). Although these histological findings were minor, they were consistent with a previous range-finding study where gastric erosion was seen in both sexes at doses ≥ 20 mg/kg/day and indicate that MK-239 acts as a gastrointestinal irritant in dogs. The absolute and/or relative ovary weights of 20 mg/kg/day females were significantly lower than controls, although this effect was not considered toxicologically significant since it was not dose-related and had no histological correlates. The transiently lower weight gains in dogs given 20 mg/kg/day (week 1 and/or 4 in both sexes; $p<0.05$ or 0.01) were likely due to the diarrhea and/or vomiting; the overall 13-week body-weight gain was comparable to controls.

The NOAEL for both male and female dogs was 2 mg/kg/day. The LOAEL was 10 mg/kg/day based on an increased incidence of diarrhea and/or vomiting in males and females. The actual dosages the high- and mid-dose animals received are uncertain because some of the compound was likely regurgitated.

b) Chronic Toxicity

Dogs

In a chronic toxicity study (MRID 43309315), MK-239 Technical (98.9% a.i.) was administered to groups of 5 male and 5 female beagle dogs orally via gelatin capsules. The doses were 0, 1, 6, or 20 mg/kg of body weight/day and were administered 7 days/week for 12 months (52 weeks).

No unscheduled mortalities occurred during the study. Incidences of vomiting food and diarrhea/loose stool were increased in the males and females from the 6 and 20 mg/kg/day groups. There were no statistically significant changes in mean body weight or mean body weight gain, although decreased body weight gain was observed in males and females (57% and 50% of control, respectively) during the first week of treatment. Overall body weight gain was decreased in males at 20 mg/kg/day (83% control) and in all treated females (69%, 75%, 75% of control in 1, 6 and 20 mg/kg/day groups, respectively). The lack of statistical significance and dose response in females makes this finding questionable toxicologically. The ophthalmoscopic examinations, hematology, clinical chemistry and urinalysis demonstrated no changes of toxicological importance. The absolute and relative prostate weights were decreased by 40.5 and 35.9%, respectively, and absolute and relative weights testis were increased by 15.4 and 25%, respectively, in the 20 mg/kg/day group. The absolute and relative adrenal weights in the males from the 20 mg/kg/day group were nonstatistically significantly increased, 7.4 and 20.0%, respectively. Gross pathology exhibited thickened gastric mucosa in the pyloric region in 1 and 2 females from the 6 and 20 mg/kg/day groups, respectively. Histopathological evaluation revealed erosion in the pyloric region in 1/5 females from the 6 and 20 mg/kg/day groups, chronic gastritis in the pyloric region in 1/5 males and 1/5 females at 6 mg/kg/day and in 2/5 males and 2/5 females at 20 mg/kg/day groups. Focal cystic acinar dilatation in the prostate was slightly increased at 20 mg/kg/day (1/5, 1/5, 1/5 and 3/5 in males at 0, 1, 6 and 20 mg/kg/day males,

respectively). **Based on the incidences of vomiting and diarrhea/loose stools and thickened gastric mucosa and chronic gastritis in the pyloric region, the LOEL is 6 mg/kg/day and the NOEL is 1 mg/kg/day.**

Rats and Mice

The chronic rat and mouse studies conducted with tebufenpyrad are discussed previously in the Evaluation of Carcinogenicity Studies section.

5. Mode of Action Studies

There are no mode of action studies available at this time.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity

The CARC concluded that tebufenpyrad showed suggestive evidence of carcinogenicity due to the following:

- Evidence of carcinogenicity was seen in the liver of one species and one sex only (i.e, **benign liver tumors were seen in male Fischer 344 rats only**). Male rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 300 ppm dose group with the controls, for hepatocellular adenomas, both at $p < 0.01$. The incidence of hepatocellular adenomas in males was 0/54, 0/55, 0/53, 4/54, and 10/54 for the 0, 5, 20, 150, or 300 ppm dose levels, respectively. The incidence at the high dose (300 ppm; 19% versus 0% in the controls) was outside the historical control ranges (0-8% [intercurrent control] and 0-12% [historical control]). The CARC considered the increase in liver tumors to be treatment-related in males. No hepatocellular carcinomas were observed in any group, including controls.

- Female rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 150 ppm dose group with the controls, for hepatocellular adenomas, both at $p< 0.05$. **However, no dose-related increase in these tumors was noted at the high dose (300 ppm) in female rats.** The incidence of hepatocellular adenomas in females was 0/53, 2/53, 0/54, 5/54, and 3/54 for the 0, 5, 20, 150, or 300 ppm dose levels, respectively. The incidence at 150 ppm (9% versus 0% controls) was just outside the historical control range (0-8%); and the incidence at 300 ppm (6% versus 0% controls) was within the historical control range (0-8%). The CARC considered these benign tumors to be equivocal. No hepatocellular carcinomas were observed in any group,

including controls.

- It was concluded that the dose levels tested were adequate, but not excessive, in both sexes to assess the carcinogenicity of tebufenpyrad in rats. This conclusion was based on decreased body weight gains in males (21%) and females (33%), clinical chemistry changes (increased alkaline phosphatase activity in both sexes), increased absolute and relative liver weights, and liver hypertrophy. These results are also supported by increased albumin/globulin ratios seen in both sexes and by the results of the subchronic feeding study in rats.

- **There was no treatment-related increase in any tumors in male and female mice.**

- In mice, dosing at the highest dose (1000 ppm) was considered by the CARC to be adequate, but not excessive, in both sexes based on decreased body weight and body weight gain in males and females (61-75% of controls) after 52 and 78 weeks of treatment, decreased food efficiency, and a dose-related increased incidence of stomach dysplasia in both sexes which was associated with thickening of the stomach walls in males at 1000 ppm.

2. Mutagenicity

- Tebufenpyrad was not mutagenic in bacterial or mammalian cell gene mutation assays. However, tebufenpyrad induced weak but reproducible clastogenic effects in human lymphocytes after prolonged exposure to cytotoxic concentrations. There was no increase in the frequency of micronucleated PCEs in bone marrow and no induced DNA damage in mammalian cells or in bacteria. Based on the findings the level of concern for in vitro clastogenesis is low because it was only seen after prolonged exposure to cytotoxic concentrations and was not manifested in the in vivo cytogenetic assay up to lethal doses. The submitted studies were acceptable and satisfy the guideline requirements for mutagenicity data. No further testing is required at this time. The Committee has no concern for mutagenicity.

3. Structure Activity Relationship

- No appropriate structural analogues were located for comparison purposes.

4. Mode of Action Studies

- There are no mode of action studies available at this time.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July, 1999), the Committee classified tebufenpyrad into the category **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"** by the oral route based on the following weight-of-the-evidence considerations:

(i) Benign liver tumors (hepatocellular adenomas) were seen in male rats only. The findings in female rats were equivocal. No hepatocellular carcinomas were observed in any group of males or female rats, including controls. There was no treatment-related increase in any tumors in male and female mice.

(ii) The Committee has no concern for mutagenicity of tebufenpyrad.

(iii) There is a lack of data on structure activity relationships and the mode of action.

VII QUANTIFICATION OF CARCINOGENIC POTENTIAL

The quantification of human cancer risk is not required.

VIII. BIBLIOGRAPHY

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Chemical:	**1H-Pyrazole-5-carboxamide, 4-chloro-N-((**
PC Code:	**090102**
HED File Code	**21200 CARC**
Memo Date:	**07/15/2002**
File ID:	**00000000** TKR050025
Accession Number:	**412-03-0016**

HED Records Reference Center
09/30/2002